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## **Editorial commentary: the irreversibility of HIV drug resistance**

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# The Irreversibility of HIV Drug Resistance

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(See the Major Article HIV/AIDS by Mbisa et al on pages 829–36.)

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Transmission of drug-resistant pathogen strains is an almost universal threat to treatment success in individual patients and to the utility of drugs at the population level. In the case of human immunodeficiency virus (HIV) in resource-rich settings, a combination of measures—including baseline resistance testing, potent regimens with high genetic barrier, close surveillance of therapy success, and introduction of new drug classes—has been uniquely successful in restricting the prevalence of transmitted drug resistance (TDR) to levels below 10%–15% [1–3]. Going beyond this success and completely eradicating the transmission of drug-resistant HIV has, however, proven to be challenging so far: Overall levels of HIV TDR in industrialized countries have decreased only weakly or not at all over the last 15 years despite strong reductions of the frequency of therapy failure

and of the emergence of drug resistance in treated individuals [2, 4]. This pattern can be explained by the hypothesis that by now, in these settings, untreated patients are the major source of HIV TDR [5]. Thus, drug-resistant strains can maintain themselves in the untreated population and are thereby not dependent on treatment failure. A key factor in this process are the slow reversion rates of many TDR mutations, which in turn are due to their low fitness costs [6, 7]. Accordingly, clear decreases in TDR have been observed for high-fitness-cost nucleoside reverse transcriptase inhibitor (NRTI) mutations such as M184V [2]. These mutations revert quickly in the absence of drug pressure and hence disappear as TDR as soon as they no longer emerge in treatment-failing patients. However, such high-cost mutations have never been very frequent among TDR HIV, and have almost vanished in the course of the recent treatment improvements. As a consequence, the bulk of TDR is composed of low-cost mutations that can successfully circulate in treatment-naïve patients.

The study by Mbisa et al [8], in the current issue of *Clinical Infectious Diseases*, tests and eventually strengthens this hypothesis by using phylogenetic and phylodynamic approaches to analyze HIV type 1 subtype B sequence data from the UK HIV Drug Resistance Database, one of the most representative databases of its kind. The phylogenetic analysis goes beyond the standard description of prevalence of

resistance mutations by capturing their occurrence in the context of the transmission network. This relies on the intuition that viruses that are close on the phylogeny are likely to be close on the transmission chain. Hence, in well-sampled populations, the closest neighbors on a phylogeny are potential transmission sources. Accordingly, an isolated occurrence of TDRs on the HIV phylogeny would imply frequent emergence in treatment-failing patients and infrequent transmission, whereas a strong clustering would suggest long transmission chains of TDR. The authors determined those patterns for the most frequent TDR mutations against NRTIs (variants/revertants at amino acid 215 in the reverse transcriptase [RT]), nonnucleoside reverse transcriptase inhibitors (NNRTIs) (103N in RT), and protease inhibitors (90M in the protease [PR]). In all 3 cases, they found that the resistance mutations observed in treatment-naïve patients formed large transmission clusters, suggesting ongoing transmission in the treatment-naïve population rather than frequent emergence in treatment-failing patients. This was further assessed in the phylodynamic part of the analysis. Here, the sequence data were used to estimate for the larger TDR transmission chains their time of origin and the basic reproductive number,  $R_0$ . This analysis revealed  $R_0$  values clearly >1 (range, 1.3–2.8), supporting the sustainable transmission of these TDR strains. Furthermore, most of these transmission chains originated in

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the early 2000s, indicating long-term, ongoing transmission. The clearest case for treatment-independent transmission is provided by the 90M mutation in the protease. The 90M mutation formed the largest cluster in this study (15 patients), which originated around 2003, but transmission in this cluster occurred mostly after 2005. As the drugs (saquinavir and nelfinavir) against which 90M confers resistance were almost out of use by that time, the clustering of 90M cannot be explained by several treatment failure events occurring along the transmission chain. This of course implies that the transmission of 90M has no clinical implication beyond being a showcase for the persistence of resistance mutations at the population level. The authors observed, however, similar degrees of clustering for the 103N mutation, which is arguably the TDR that leads and will lead globally to most treatment failures.

The reconstruction and analysis of transmission chains by molecular methods allows a unique perspective on the spread of infectious agents, but it also has its limitations and this study is no exception. At the most basic level, there is no one-to-one relation between sequences and transmission network—and, accordingly, determining transmission chains from sequence data depends on ad hoc thresholds and criteria. For the most part, these criteria (such as the 1.5% distance threshold) are well established, but it is nevertheless important to keep in mind that alternative—and equally defensible—criteria would have led to different transmission clusters. More critical for the present study is that the main phylogenetic analysis was conducted using only sequences containing TDR. The omission of control sequences without TDR implies that it cannot be excluded that some of the transmission chains that appear to consist only of TDR viruses might contain intermediate links consisting of strains without TDR, which were not included in the analyzed dataset. Such clusters would then have to be interpreted not as long sustained

transmission chains of TDR, but as several independent emergence events associated with treatment failures followed by much smaller TDR transmission chains. Indeed, a sensitivity analysis, in which 1000 randomly selected sequences from the UK Drug Resistance Database were combined with the 1140 TDR-containing sequences, exhibited a lower degree of clustering of TDR. This effect would probably have been even stronger if the entire UK Drug Resistance Database (>25 000 subtype B sequences) would have been included as controls. Thus, some of the observed clustering is spurious and the length of TDR transmission chains is probably lower than estimated by this study. We expect, however, that this overestimation is not too serious and that, at least qualitatively, the findings are robust to this approximation (just to mention 2 reasons: first, the 1.5% distance thresholds protects against excessive spurious clustering; second, treatment failure is generally relatively rare and can be practically excluded as a source for 90M after 2005). Finally, it should be noted that the phylodynamic analysis was only performed for the larger clusters and, accordingly, the  $R_0$  estimates suggesting self-sustained TDR transmission apply only to these clusters. This implies a selection bias because large clusters correspond to those instances where HIV could spread successfully, whereas small clusters correspond to limited transmission. Hence, the  $R_0$  estimates derived from the large clusters may overestimate the number of secondary infections caused by one TDR case in the entire population.

Despite these almost unavoidable limitations of molecular epidemiology, the study clearly improves and extends the evidence for sustained treatment-independent transmission of drug-resistant HIV: It confirms a previous analysis from the Swiss HIV Cohort Study, which found that 85% of TDR in men who have sex with men was transmitted by therapy-naïve patients [5], and adds new types of evidence ( $R_0$ , timing of transmission chains). These findings have 2 key implications for

HIV public health. First, they support that a further reduction and eventual elimination of TDR in industrialized countries cannot rely only on the prevention of treatment failure alone but also needs to address transmission among untreated individuals. This would thus add one further reason in favor of early detection and treatment of HIV. Second, TDR has exhibited consistent increases in resource-limited settings over the last years, with the 103N mutation being the dominant mutation in terms of both prevalence and of likely clinical impact. Currently, first-line treatment in almost all of sub-Saharan Africa relies on NNRTIs, which would be dramatically affected by a high prevalence of 103N [9]. The results of the present study argue for early action to prevent the spread of this mutation because its ability to transmit even in the absence of drug pressure predicts that it may be very hard to curb it once it (and any other low-fitness-cost mutation) has reached a high prevalence. This might even affect other mutations than the 103N given that in resource-limited settings viral load monitoring is scarce and patients often stay for long periods on failing regimens, leading to extensive accumulation of resistance mutations [10]. This and the variability in fitness costs and reversion rates even for the same TDR in different genetic backgrounds [6] imply that the likelihood that in the future even high-fitness-cost mutations may convert into low-fitness-cost mutations and may be fixed in these populations should not be underestimated. Hence, strategies to use viral load monitoring and to use drugs with high genetic barriers earlier need to be explored. Overall, this study demonstrates the often underestimated ability of antimicrobial resistance to persist and spread, which underlines the need for early preventive action while the resistance problem is still small.

## Notes

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